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The Effect of Smoking on Allogeneic Transplant Outcomes

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Using the Center for Internaitonal Blood and Marrow Transplant Research (CIBMTR) data, we compared the transplant outcomes of patients with chronic myelogenous leukemia (CML) who were nonsmokers (NS) and past or current smokers (PCS). There were 2193 NS and 625 PCS who received matched sibling and unrelated donor allografts for CML in first chronic phase. We looked for dose effects and identified low and high dose smoking groups (>10 pack years, >1 pack per day). Outcomes were adjusted for known prognostic variables including the European Group for Blood and Marrow Transplant (EBMT) risk score. In multivariate analyses of sibling allograft recipients, relapse risk (RR) was higher (RR = 1.67, $P = .003$) in smokers than NS, but the dose effects were not consistent. High-dose smokers experienced a 50% treatment-related mortality (TRM) versus 28% in the NS group at 5 years on univariate analysis, and the RR was 1.57 ($P = .005$) on multivariate analysis. Overall survival (OS) at 5 years was 68% in NS versus 62% in the low-dose smoking group versus 50% in the high-dose smoking group ($P < .001$). Smoking did not significantly affect outcomes in unrelated donor recipients, but numbers were smaller. High-dose smoking is associated with a reduction in OS in patients having sibling allografts for CML. A prospective study with detailed demographic, pulmonary function, and quality-of-life data would improve our understanding of this issue.

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INTRODUCTION

Allogeneic stem cell transplantation is widely used to cure patients with leukemia and other hematologic conditions. Various biologic factors influence the transplant outcome of patients with chronic myelogenous leukemia (CML). These include patient age [1] (Center for International Blood and Marrow Transplant Research [CIBMTR], unpublished data), performance status at transplant [2], and body mass index [1]. Pretransplant pulmonary function may also affect overall transplant outcome and posttransplant respiratory complications [3,4]. One of the major causes of pretransplant respiratory abnormalities is cigarette smoking. Depending on the population studied, between 20% and 50% of adult allogeneic transplant candidates have a current smoking history, and many additional patients have a past smoking history. Smoking, as well as affecting pulmonary function, can influence the risk of coronary artery disease [5], and is an important cause of lung cancer (which may be increased after allogeneic transplantation) [6]. Smokers are known to have different demographics than nonsmokers (NS). They are more likely to be male, of a lower socioeconomic status [7,8], and have a higher alcohol intake [9]. In studies of the effect of smoking on health outcomes, it is possible that these associations of smoking may affect the outcomes.

No large-scale studies address the effect of smoking on transplant outcome. The CIBMTR database,

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which includes data on smoking history, is ideal for this purpose. We hypothesized that a smoking history would significantly reduce the chance of a successful transplant outcome by increasing treatment-related mortality (TRM), primarily through pulmonary complications, including infection. Relapse incidence was also studied because physicians may have altered conditioning in patients who smoke. Smoking may affect the incidence of secondary malignancies, but this study was not designed to address this issue.

We elected to study patients with CML in first chronic phase (CP1), because we hypothesized that examining the effect of smoking in a chemotherapy naïve population would "isolate" the effect of smoking. Smoking might make pulmonary complications more likely after pretransplant chemotherapy, but we wished to study the effect of smoking on transplant alone. This focus on CML also eliminated a potential source of patient heterogeneity, and the prognostic factors affecting the transplant outcome of CML patients are well described [10]. We analyzed sibling and unrelated donor transplants separately, as the latter has a greater TRM and may have received higher doses of total body irradiation (TBI).

There are numerous practical implications of performing this study. Transplant teams will be able to inform better patients who smoke about the chances of a successful outcome. The study may generate information that enables transplanters to modify conditioning regimens to increase the chance of a successful outcome. Finally, when the causes of treatment failure are determined, transplanters may be able to direct their supportive care efforts to preventing specific problems.

PATIENT SELECTION AND INCLUSION CRITERIA

Patient data for this study were obtained from the CIBMTR. More than 500 participating centers register consecutive allogeneic transplants to CIBMTR. Detailed demographic and clinical data are collected on a sample of registered patients. Compliance is monitored by on-site audits. Computerized error checks, physician reviews of submitted data, and on-site audits of centers ensure the quality of data.

This study included all patients between 1990 and 2004, aged 18 years and above, who received HLA-identical sibling or matched unrelated donor (MUD) allogeneic transplants for CML in CP1 for whom a smoking history was known. Patients received busulphan (Bu) and cyclophosphamide (Cy) or TBI and Cy for conditioning. Graft type was restricted to bone marrow (BM) or peripheral blood (PB). Graft-versus-host disease (GVHD) prophylaxis was restricted to cyclosporine (CsA) and methotrexate (MTX), tacrolimus and MTX, T cell depletion, or CsA and other immunosuppressive agents. Patients who received low-dose oral Bu prior to transplant were excluded.

The number of patients with CML in CP1 aged >18 years who had allografts reported to the CIBMTR between 1990 and 2004 was 5461. A total of 5022 patients received a sibling or MUD allograft of BM or PB. We only included the 4409 receiving Cy/TBI or Bu/Cy conditioning and excluded the patients who had received prior low-dose Bu, leaving 3880 patients. We confined our study to 3793 patients with specific types of GVHD prophylaxis (defined before). Finally, we had quantitative smoking information for 2818 of these patients.

Smoking Data

Patients were categorized as NS or past or current smokers (PCS) based on self-reported responses extracted from medical notes by data managers completing the CIBMTR forms. The questions, which asked about smoking history, varied slightly in 1989, 1995, and 2002. However, all questionnaire versions enquired about duration and number of cigarettes per day. The quantitative data regarded number of years smoked and amount per day (<1 pack, 1 pack and >1 pack) enabling us to compare the major outcomes in these groups and look for a dose effect. In this study PCS are termed "smokers." We divided smokers into 2 "doses": high-dose smokers had accumulated >10 pack years and smoked >1 pack per day, and low-dose smokers had ≤10 pack years or ≤1 pack per day.

Statistical Methods

Patient-, disease-, and treatment-related variables for patients in the 3 smoking groups were compared using chi-square test for categoric variables and the Kruskal-Wallis test for continuous variables. *P*-values for pair-wise comparison were adjusted using Bonferroni correction.

The primary endpoints were relapse, TRM, disease-free survival (DFS), and overall survival (OS). The event relapse was defined as occurrence of CML (clinical and/or cytogenetic) posttransplant. TRM was defined as death within 28 days posttransplant or death without CML relapse. Smoking may affect the incidence of fungal infection, but because our data does not allow us to verify this diagnosis, this was not an endpoint of the study.

Probabilities of TRM and relapse were calculated using the cumulative incidence function method [11]. Treatment-related death and relapse were the competing events. Data on patients without either competing event were censored at last follow-up. For analyses of survival, death from any cause was considered an event and surviving patients were censored at last follow-up.

For analyses of DFS, we considered relapse or death an event.

All *P* values were 2 sided, and a value of <.05 was considered statistically significant.

Cox proportional hazards models were used to adjust for patient-related, disease-related, and treatment-related covariates. A main effect term for smoking was forced into the model. The remaining covariates were included using a stepwise forward selection technique with a value of $P \leq .05$ as the criterion for inclusion in the final models. Other variables considered in the models include: recipient age, sex, region of transplant center, performance score, white blood cells (WBC) at diagnosis, body mass index prior to transplant, spleen size at diagnosis, pretransplant use of hydroxyurea, interferon, or gleevec, interval from diagnosis to transplant, year of transplant, HLA matching, conditioning regimen, use of antithymocyte globulin (ATG) or alemtuzamab antibody therapy prior to transplant, use of lung shielding in radiation therapy, GVHD prophylaxis, donor age, donor-recipient sex match, source of graft, European Group for Blood and Marrow Transplant (EBMT) risk score, cytomegalovirus (CMV) status, and coexisting disease. The EBMT risk score is a scoring system designed by the European Group for Blood and Marrow Transplantation to predict the survival after allogeneic transplant for CML patient [10]. Higher score indicates a lower probability of survival. The CIBMTR does not collect sufficient data to calculate a Sokol score. Pulmonary function test data is not routinely collected by CIBMTR.

The proportional hazards assumption for each variable was examined using time-varying covariate and graphical approaches. Stratified proportional hazards models were used when variables with nonproportional hazards were identified. No significant interactions between smoking and other explanatory variables were found. There were no statistically significant center effects. In addition to the comparison of NS with PCS, we also considered models with subgroups of PCS based on years smoked and average packs per day. The cut point for years smoked (≤10 years versus >10 years) was selected based on plots of the Martingale residuals. Because age is related to duration of smoking, we tested for confounding by analyzing the subgroup of patients 30 years of age and older to determine consistency of effect relative to the group of all patients. Analyses were performed with the use of SAS software, version 9.1 (SAS Institute, Cary, NC).

Because data regarding smoking exposure was limited, we considered 5 models in looking for an effect of smoking. First, we simply compared PCS and NS. Second, PCS were divided according to duration of smoking (≤10 years and >10 years). Third, the average number of packs per day was divided into <1 pack, 1 pack, >1 pack. Fourth, we compared smokers with >10 pack years and ≤10 pack years. In the fifth model, we combined models 2, 3, and 4 and compared low- and high-dose smokers as stated above. This results and discussion will be focused on the fifth model.

RESULTS

Patient Characteristics in Sibling Allograft Recipients

Table 1 shows the characteristics of patients >18 years with CML who had sibling donor transplants, and compares NSs and those who are low- or high-dose smokers. Table 2 shows similar data for recipients of unrelated donor transplants. We divided smokers into 2 "doses." In the sibling allograft recipients, high-dose smokers (n = 94) had accumulated >10 pack years and smoked >1 pack per day, and low-dose smokers (n = 370) had ≤10 pack years or ≤1 pack per day. Overall, the median number of years of smoking was 15 years, and 22% smoked >1 pack per day.

Overall, in the sibling allograft group, high-dose smokers compared to NS were slightly older, more were male (72% versus 54%), had a lower diagnostic white cell count (WCC), slightly more were female-to-male transplants (27% versus 22%) and had a higher EBMT risk score (83% versus 66% were 2-4, $P < .001$). Fewer high-dose smokers had no coexisting medical diseases (52% versus 78%, $P < .001$).

There was no evidence that the transplants were performed differently in smokers; cytotoxic drug doses were similar in the 2 groups as was the dose of TBI, and there was no difference in lung shielding.

Major Outcomes on Univariate Analysis

In the matched sibling donor group, survival at 5 years was significantly lower in the high-dose smoker group (50%) compared to the NS and low-dose smoker groups (68% and 62%, respectively) (Table 3 and Figure 1). DFS was 20% lower in the high-dose group than the BS group (44% versus 64%, $P < .001$). TRM at 5 years was similar in the nonsmoker and low-dose smoker groups (28% versus 32%), but considerably higher in the high-dose smoker group (50%, $P < .001$). The absolute 5-year incidence of relapse is similar in the NS and low- and high-dose smoker groups (8% versus 10% vesus 6%, respectively). There are no differences in the incidence of bronchopneumonia, interstitial pneumonitis (IP), and broncholitis obliterans among the 3 groups (Table 3). There were no significant interactions between smoking and conditioning regimen ($P = .309$ for TRM) or between smoking and GVHD prophylaxis ($P = .310$ for TRM).

Although TRM was higher and DFS and OS were lower in the high-dose recipients of unrelated donor

Table 1. Characteristics of Patients ≥18 Years Receiving HLA-Identical Sibling Donor Rransplants for CML in First Chronic Phase, Reported to the CIBMTR, 1990-2004

			Smokers			
	Nonsmokers			Low Dose*		High Dose*
Variables	N	N (%)	N	N (%)	N	N (%)
Number of patients	1649		370		94	
Age at transplant, years, median (range)	1649	37 (18-61)	370	38 (18-66)	94	45 (22-58)
Age at transplant, years	1649		370		94	
18-29		419 (25)		67 (18)		6 (6)
30-39		580 (35)		134 (36)		22 (23)
40-49		466 (28)		115 (31)		48 (51)
≥ 50		184 (11)		54 (15)		18 (19)
Male	1649	888 (54)	370	262 (71)	94	68 (72)
Region	1648		370		94	
United States		499 (30)		126 (34)		53 (56)
Canada		60 (4)		14 (4)		8 (9)
Europe		594 (36)		141 (38)		20 (21)
Asia		143 (9)		20 (5)		4 (4)
Australia/New Zealand		88 (5)		13 (4)		3 (3)
Mideast/Africa		139 (8)		12 (3)		3 (3)
Central/South America		125 (8)		44 (12)		3 (3)
Karnofsky score (< 90%)	1637	171 (10)	366	42 (11)	92	15 (16)
Number of packs per day			370		94	
≤ 1		–		363 (98)		–
> 1		–		7 (2)		94 (100)
Number of years smoked, median (range)		–	370	12 (1-43)	94	20 (5-44)
Smoking pack-year,median (range)		–	370	10 (<1-43)	94	34 (12-140)
Smoking pack-year,			370		94	
≤ 10 pack-year		–		222 (60)		–
> 10 pack-year		–		148 (40)		94 (100)
Body mass index, kg/m2	1635		369		94	
≤ 22		380 (23)		69 (19)		19 (20)
22-30		1012 (62)		238 (64)		59 (63)
> 30		243 (15)		62 (17)		16 (17)
White cell count at diagnosis, 10^9/L, median (range)	1529	145 (1-800)	347	114 (7-650)	89	96 (4-387)
White cell count at diagnosis, 10^9/L	1529		347		89	
< 50		282 (18)		91 (26)		26 (29)
50-100		290 (19)		68 (20)		24 (27)
> 100		957 (63)		188 (54)		39 (44)
Spleen size at diagnosis	1477		342		81	
Normal		467 (32)		127 (37)		31 (38)
Enlarged		1010 (68)		215 (63)		50 (62)
Coexisting diseases	1646		369		94	
Cardiac and pulmonary		9 (1)		2 (1)		4 (4)
Cardiac		107 (7)		32 (9)		14 (15)
Pulmonary		28 (2)		12 (3)		7 (7)
Other		214 (13)		60 (16)		20 (21)
None		1288 (78)		263 (71)		49 (52)
Pretransplant therapy for CML						
Hydroxyurea	1634	1510 (92)	368	333 (90)	94	78 (83)
Interferon	1205	578 (48)	269	127 (47)	75	33 (44)
Imatinib	1648	50 (3)	370	9 (2)	94	4 (4)
Time from diagnosis to transplant, months, median (range)	1649	8 (<1-127)	370	9 (1-72)	94	7 (2-99)
Time from diagnosis to transplant, months	1649		370		94	
< 6		522 (32)		108 (29)		38 (40)
6-11		591 (36)		138 (37)		31 (33)
12-23		380 (23)		90 (24)		18 (19)
≥ 24		156 (9)		34 (9)		7 (7)
EBMT risk score	1647		370		94	
0-1		572 (35)		92 (25)		16 (17)
2		717 (44)		171 (46)		48 (51)
3		322 (20)		91 (25)		26 (28)
4		36 (2)		16 (4)		4 (4)
Year of transplant	1649		370		94	
1990-1994		746 (45)		155 (42)		44 (47)
1995-1999		655 (40)		173 (47)		44 (47)
2000-2004		248 (15)		42 (11)		6 (6)
Conditioning regimen	1649		370		94	

(Continued)

Table 1. (*Continued*)

	Nonsmokers		Smokers			
			Low Dose*		High Dose*	
Variables	N	N (%)	N	N (%)	N	N (%)
TBI/Cy ± other		591 (36)		124 (34)		36 (38)
Bu/Cy ± other (no TBI)		1058 (64)		246 (66)		58 (62)
Dose of Cy,† mg/kg	1432		320		76	
120		1267 (88)		279 (87)		65 (86)
200		165 (12)		41 (13)		11 (14)
Dose of Bu, mg/kg	1627		366		93	
No Bu		591 (36)		124 (34)		36 (39)
< 12		59 (4)		6 (2)		5 (5)
12-16		304 (19)		72 (20)		23 (25)
16-17		613 (38)		157 (43)		25 (27)
≥ 17		60 (4)		7 (2)		4 (4)
Dose of TBI, cGy	1603		352		86	
Non-TBI		1058 (66)		246 (70)		58 (67)
< 1300		421 (26)		79 (22)		18 (21)
≥ 1300		124 (8)		27 (8)		10 (12)
GVHD prophylaxis	1649		370		94	
T depl ± other		102 (6)		25 (7)		9 (10)
FK506 ± other		58 (4)		10 (3)		4 (4)
MTX + CsA ± other		1324 (80)		293 (79)		66 (70)
CsA ± other (no MTX)		165 (10)		42 (11)		15 (16)
Donor age	1580		352		88	
≤ 29		460 (29)		73 (21)		8 (9)
30-39		534 (34)		123 (35)		25 (28)
40-49		405 (26)		98 (28)		40 (45)
≥ 50		181 (11)		58 (16)		15 (17)
Sex match	1647		370		94	
Male into male		523 (32)		141 (38)		43 (46)
Male into female		405 (25)		55 (15)		16 (17)
Female into male		365 (22)		121 (33)		25 (27)
Female into female		354 (21)		53 (14)		10 (11)
Donor-recipient CMV status	1555		350		91	
− / −		391 (25)		89 (25)		24 (26)
− /+		200 (13)		45 (13)		14 (15)
+/ −		183 (12)		40 (11)		10 (11)
+/+		781 (50)		176 (50)		43 (47)
Graft type	1649		370		94	
BM		1331 (81)		301 (81)		78 (83)
PB ± BM		318 (19)		69 (19)		16 (17)
Use of ATG or Campath	1627	15 (1)	365	3 (1)	94	4 (4)
Lung shielding in radiation therapy	1587	262 (17)	360	50 (14)	92	11 (12)
Follow-up of surviving patients, month	1649	91 (2-209)	370	98 (1-199)	94	115 (19-193)

CML indicates chronic myelogenous leukemia; TBI, total body irradiation; Cy, cyclophosphamide; Bu, busulfan; GVHD, graft-versus-host disease; MTX, methotrexate; CsA, cyclosporine; BM, bone marrow; PB, peripheral blood; CIBMTR, Center for International Blood and Marrow Transplant Research; ATG, antithymocyte globulin; EBMT, European Group for Blood and Marrow Transplant.
Duration of follow-up:
Nonsmoker: ≥1 year = 73%; ≥3 year = 61%; ≥ 5 year = 50%.
Low-dose smoker: ≥ 1 year = 69%; ≥3 year = 59%; ≥ 5 year = 49%.
High-dose smoker: ≥ 1 year = 70%; ≥3 year = 46%; ≥ 5 year = 45%.
*Low-dose smokers = smoking ≤10 pack-years or >10 pack-years with ≤ 1 pack/day; high-dose smokers = smoking >10 pack-years with >1 pack/day.
†Cy dose range 100-150 mg/kg classified as 120 mg/kg; Cy dose ≥150 mg/kg classified as 200 mg/kg.

grafts, this was not significant (*P*-value = .2, .3, and .3 respectively); this may relate to there being only 30 such patients.

Multivariate Analysis of Major Outcomes in Sibling Allograft Group

Relapse

PCS overall had a higher relative risk (RR) of relapse (RR = 1.67, *P* = .003). There was some evidence of a dose effect, although this was not consistent. More than 10 years smoking duration was associated with a higher RR of relapse; however, a higher number of packs smoked per day (data not shown) or high-dose smoking overall were not associated with a higher chance of relapse. There was no difference in the incidence of acute GVHD (aGVHD) and chronic GVHD (cGHVD) in PCS and NCS (58% versus 57% and 51% versus 50%, respectively, *P* = .60 and .46. respectively).

Table 2. Characteristics of Patients ≥18 Years Receiving Matched Unrelated Donor Transplants for CML in First Chronic Phase, Reported to the CIBMTR, 1990-2004

			Smokers			
	Nonsmokers			Low Dose*		High Dose*
Variables	N	N (%)	N	N (%)	N	N (%)
Number of patients	544		131		30	
Age at transplant, years, median (range)	544	34 (18-61)	131	37 (19-58)	30	43 (19-53)
Age at transplant, years	544		131		30	
18-29		165 (30)		30 (23)		2 (7)
30-39		214 (39)		46 (35)		8 (27)
40-49		145 (27)		45 (34)		15 (50)
≥ 50		20 (4)		10 (8)		5 (17)
Male	544	317 (58)	131	89 (68)	30	24 (80)
Region	544		131		30	
United States		173 (32)		52 (40)		19 (63)
Canada		31 (6)		8 (6)		2 (7)
Europe		245 (45)		56 (43)		7 (23)
Asia		54 (10)		13 (10)		1 (3)
Australia/New Zealand		20 (4)		1 (1)		0 (0)
Mideast/Africa		8 (1)		0 (0)		0 (0)
Central/South America		13 (2)		1 (1)		1 (3)
Karnofsky score (<90%)	535	49 (9)	131	11 (8)	30	5 (17)
Number of packs per day			131		30	
≤ 1		–		131 (100)		–
> 1		–		–		30 (100)
Number of years smoked, median (range)		–	131	15 (2-35)	30	20 (6-35)
Smoking pack-year, median (range)		–	131	10 (1-35)	30	35 (12-93)
Smoking pack-year			131		30	
≤ 10 pack-year		–		66 (50)		–
> 10 pack-year		–		65 (50)		30 (100)
Body mass index, kg/m^2	535		126		30	
≤ 22		116 (22)		31 (25)		5 (17)
22-30		338 (63)		73 (58)		17 (57)
> 30		81 (15)		22 (17)		8 (27)
White cell count at diagnosis, 10^9/L, median (range)	487	150 (4-790)	115	126 (1-779)	30	116 (19-334)
White cell count at diagnosis, 10^9/L	487		115		30	
< 50		84 (17)		34 (30)		6 (20)
50-100		83 (17)		17 (15)		7 (23)
> 100		320 (66)		64 (56)		17 (57)
Spleen size at diagnosis	452		108		26	
Normal		147 (33)		53 (49)		9 (35)
Enlarged		305 (67)		55 (51)		17 (65)
Coexisting diseases	543		131		30	
Cardiac and Pulmonary		3 (1)		0 (0)		0 (0)
Cardiac		26 (5)		8 (6)		5 (17)
Pulmonary		9 (2)		3 (2)		3 (10)
Other		78 (14)		18 (14)		5 (17)
None		427 (79)		102 (78)		17 (57)
Pretransplant therapy for CML						
Hydroxyurea	538	507 (94)	130	114 (88)	30	24 (80)
Interferon	479	308 (64)	118	86 (73)	25	17 (68)
Imatinib	543	48 (9)	131	5 (4)	30	0 (0)
Time from diagnosis to transplant, months, median (range)	544	15 (1-111)	131	16 (3-95)	30	17 (6-39)
Time from diagnosis to transplant, months	544		131		30	
< 6		50 (9)		6 (5)		0 (0)
6-11		145 (27)		38 (29)		11 (37)
12-23		180 (33)		54 (41)		14 (47)
≥ 24		169 (31)		33 (25)		5 (17)
EBMT risk score	526		122		28	
0-1		10 (2)		0 (0)		1 (4)
2		130 (25)		21 (17)		0 (0)
3		226 (43)		52 (43)		12 (43)
4		144 (27)		42 (34)		12 (43)
5		16 (3)		7 (6)		3 (11)
Year of transplant	544		131		30	
1990-1994		192 (35)		59 (45)		17 (57)
1995-1999		228 (42)		57 (44)		13 (43)
2000-2004		124 (23)		15 (11)		0 (0)

(Continued)

Table 2. (*Continued*)

	Nonsmokers		Smokers			
			L.ow Dose*		High Dose*	
Variables	N	N (%)	N	N (%)	N	N (%)
Conditioning regimen	544		131		30	
TBI/Cy ± other		409 (75)		100 (76)		26 (87)
Bu/Cy ± other (no TBI)		135 (25)		31 (24)		4 (13)
Degree of matching	538		130		29	
Well Matched		68 (13)		19 (15)		5 (17)
Partially matched		162 (30)		40 (31)		13 (45)
Mismatched		211 (39)		57 (44)		9 (31)
Unknown		97 (18)		14 (11)		2 (7)
Dose of Cy,† mg/kg	466		107		23	
120		415 (89)		93 (87)		21 (91)
200		51 (11)		14 (13)		2 (9)
Dose of Bu, mg/kg	542		129		30	
No Bu		409 (75)		100 (78)		26 (87)
< 12		13 (2)		0 (0)		0 (0)
12-16		28 (5)		6 (5)		0 (0)
16-17		85 (16)		21 (16)		3 (10)
≥ 17		7 (1)		2 (2)		1 (3)
Dose of TBI, cGy	523		124		29	
Non-TBI		135 (26)		31 (25)		4 (14)
< 1300		251 (48)		65 (52)		13 (45)
≥ 1300		137 (26)		28 (23)		12 (41)
GVHD prophylaxis	544		131		30	
T depl ± other		117 (22)		29 (22)		7 (23)
FK506 ± other		67 (12)		10 (8)		3 (10)
MTX + CsA ± other		344 (63)		87 (66)		19 (63)
CsA ± other (no MTX)		16 (3)		5 (4)		1 (3)
Donor age	465		105		24	
≤ 29		132 (28)		20 (19)		6 (25)
30-39		180 (39)		54 (51)		10 (42)
40-49		134 (29)		26 (25)		5 (21)
≥ 50		19 (4)		5 (5)		3 (13)
Gender match	532		124		28	
Male into male		213 (40)		57 (46)		12 (43)
Male into female		122 (23)		30 (24)		3 (11)
Female into male		97 (18)		26 (21)		10 (36)
Female into female		100 (19)		11 (9)		3 (11)
Donor-recipient CMV status	513		121		26	
− / −		183 (36)		39 (32)		9 (35)
− /+		116 (23)		40 (33)		4 (15)
+/ −		81 (16)		11 (9)		4 (15)
+/+		133 (26)		31 (26)		9 (35)
Graft type	544		131		30	
BM		505 (93)		127 (97)		29 (97)
PB ± BM		39 (7)		4 (3)		1 (3)
Use of ATG or Campath	505	172 (34)	121	33 (27)	28	8 (29)
Lung shielding in radiation therapy	505	170 (34)	119	43 (36)	29	13 (45)
Follow-up of surviving patients, months	544	79 (4-194)	131	90 (4-195)	30	109 (13-157)

CML indicates chronic myelogenous leukemia; TBI, total body irradiation; Cy, cyclophosphamide; Bu, busulfan; GVHD, graft-versus-host disease; MTX, methotrexate; CsA, cyclosporine; BM, bone marrow; PB, peripheral blood; CIBMTR, Center for International Blood and Marrow Transplant Research; ATG, antithymocyte globulin; EBMT, European Group for Blood and Marrow Transplant; CMV, cytomegalovirus.
Duration of follow-up:
Nonsmoker: ≥1 year = 55%; ≥3 year = 43%; ≥ 5 year = 31%.
Low-dose smoker: ≥1 year = 53%; ≥3 year = 41%; ≥ 5 year = 33%.
High-dose smoker: ≥1 year = 54%; ≥3 year = 34%; ≥ 5 year = 27%.
*Low-dose smokers = smoking ≤10 pack-years or >10 pack-years with ≤1 pack/day; high-dose smokers = smoking >10 pack-years with >1 pack/day.
†Cy dose range 100-150 mg/kg classified as 120 mg/kg, Cy dose ≥150 mg/kg classified as 200 mg/kg.

Treatment-related mortality

A multivariate analysis comparing TRM in sibling allograft recipients is shown in Table 4. The relative risk of TRM is not different between NS and PCS overall. However, high-dose smoking was strongly associated with a higher TRM (RR = 1.57, $P = .005$).

The effect of smoking on risk of TRM is significantly increased among 28-day survivors (RR = 1.65, $P = .002$), and, importantly, remains elevated for 100-day survivors (RR = 1.81, $P = .002$) and 1-year survivors (RR = 3.29, $P < .001$), suggesting a consistent effect over time.

Table 3. Univariate Outcome of Patients ≥18 Year Receiving Allogeneic Transplants for CML in First Chronic Phase, Reported to the CIBMTR, 1990-2004

	HLA-Matched Siblings Donor							Unrelated Donor						
Smoker Group* Outcomes	N	Never (95% CI)	N	Low Dose (95% CI)	N	High Dose (95% CI)	*P*-Value	N	Never (95% CI)	N	Low Dose (95% CI)	N	High Dose (95% CI)	*P*-Value
Relapse	1565		347		88			514		119		30		.837
100 days		1 (0-1)		1 (0-3)		0	.013		1 (0-2)		1 (0-3)		0	
1 year		3 (2-4)		6 (4-9)		3 (1-8)			3 (2-5)		3 (1-8)		0	
3 years		6 (5-8)		9 (6-12)		3 (1-8)			6 (4-8)		5 (2-10)		0	
5 years		8 (7-9)		10 (7-14)		6 (2-12)			7 (5-9)		5 (2-10)		0†	
TRM	1565		347		88		<.001	514		119		30		.200
100 days		12 (10-13)		11 (8-15)		17 (10-26)			23 (19-26)		19 (13-27)		33 (18-51)	
1 year		22 (20-25)		24 (20-29)		28 (20-38)			41 (37-46)		42 (33-51)		57 (39-74)	
3 years		27 (24-29)		29 (24-34)		41 (31-52)			46 (42-51)		48 (39-57)		64 (46-80)	
5 years		28 (25-30)		32 (27-37)		50 (40-61)			49 (44-53)		50 (41-59)		68 (50-83)	
DFS	1565		347		88		<.001	514		119		30		.293
100 days		88 (86-89)		87 (83-90)		83 (74-90)			76 (72-80)		80 (72-86)		67 (49-82)	
1 year		75 (73-77)		70 (65-75)		68 (58-77)			56 (51-60)		54 (45-63)		43 (26-61)	
3 years		67 (65-69)		63 (57-68)		55 (45-66)			48 (43-52)		47 (37-56)		36 (20-54)	
5 years		64 (62-67)		58 (52-63)		44 (33-54)			44 (40-49)		44 (35-54)		32 (17-50)	
Bronchopneumonia	1575		363		88		.602	512		129		30		.963
100 days		10 (8-11)		12 (9-16)		11 (6-19)			16 (13-19)		15 (9-21)		10 (2-23)	
1 year		18 (16-20)		17 (14-21)		19 (11-28)			25 (21-29)		26 (18-34)		23 (10-40)	
3 years		23 (21-25)		23 (19-28)		26 (17-36)			30 (26-35)		29 (21-37)		31 (16-48)	
5 years		25 (22-27)		26 (21-31)		26 (17-36)			30 (26-35)		31 (23-40)		31 (16-48)	
IPN	1634		359		94		.018	534		129		29		.671
100 days		6 (5-7)		8 (5-11)		14 (8-22)			13 (10-16)		12 (7-19)		14 (4-28)	
1 year		11 (10-13)		12 (9-15)		21 (13-30)			20 (16-23)		17 (11-25)		21 (8-37)	
3 years		12 (11-14)		14 (10-18)		21 (13-30)			21 (17-24)		18 (12-26)		25 (11-42)	
5 years		13 (11-15)		15 (11-19)		21 (13-30)			21 (18-25)		18 (12-26)		25 (11-42)	
BO	1320		298		78		.731	444		104		25		.473
100 days		0 (0-1)		0		1 (0-5)			0 (0-1)		0 (0-100)		0 (0-100)	
1 year		2 (1-3)		3 (1-5)		3 (0-7)			3 (2-5)		2 (0-6)		0 (0-100)	
3 years		4 (3-5)		4 (2-7)		4 (1-10)			5 (3-7)		2 (0-6)		8 (0-27)	
5 years		4 (3-6)		5 (2-8)		6 (2-13)			5 (3-8)		2 (0-6)		8 (0-27)	
Overall survival	1649		370		88		<.001	512		119		30		.278
100 days		88 (86-89)		88 (84-91)		83 (74-90)			76 (72-79)		80 (71-86)		67 (49-82)	
1 year		76 (74-78)		73 (69-78)		72 (62-80)			56 (52-60)		56 (47-65)		43 (26-61)	
3 years		70 (68-73)		66 (62-71)		59 (48-69)			50 (46-54)		48 (39-57)		36 (20-54)	
5 years		68 (66-70)		62 (57-67)		50 (40-61)			46 (41-50)		46 (37-55)		32 (17-50)	

TRM indicates treatment-related mortality; DFS, disease-free survival; IPN, interstitial pneumonitis; BO, broncholitis obliterans; CI, confidence interval.
Note: Comparing nonsmoker and low-dose smoker versus high-dose smoker in the unrelated donor group:
Relapse: *P*-value = .685.
TRM: *P*-value = .074.
Overall survival: *P*-value = .115.
*Low-dose smokers = smoking ≤10 pack-years or >10 pack-years with ≤ 1 pack/day; high-dose smokers = smoking >10 pack-years with >1 pack/day.
†No relapses were reported for the high-dose smokers in the unrelated donor group, although small sample size and high TRM are important considerations. Confidence intervals are not relevant.

DFS and OS

DFS was shorter in PCS (RR = 1.22, $P = .019$). There were clear dose effects. High-dose smokers had a significantly shorter DFS (RR = 1.52, $P = .005$, Table 4).

However, OS was only affected by high-dose smoking (RR = 1.44, $P = .015$), and this was confirmed by dose effects (Table 4). The distribution of causes of death, as reported by the hematopoietic cell transplant (HCT) centers, was similar for the related and unrelated transplant recipients (Tables 5 and 6).

We further analyzed outcomes in the group of patients with a Karnofsky score <90 at transplant and found no differences between PCS and NS (data not shown).

MUD transplant recipients

The clinical characteristics of MUD recipients are shown in Table 2 and univariate analysis of outcomes in Table 3. For these analyses we compared NS and low-dose smokers (combined) with high-dose smokers. TRM was lower in BS and low-dose smokers compared to high-dose smokers (49% versus 68%), but this was not significant ($P = .074$). Survival at 5 years in the high-dose group was 32% compared to 46% in the NS and low-dose smoker groups ($P = .115$). In the multivariate analyses, we compared NS with PCS (Table 4). There were no differences in the major outcomes (relapse, TRM, DFS, or OS) between the 2 groups. Dose effects were also tested and no significant differences were found.

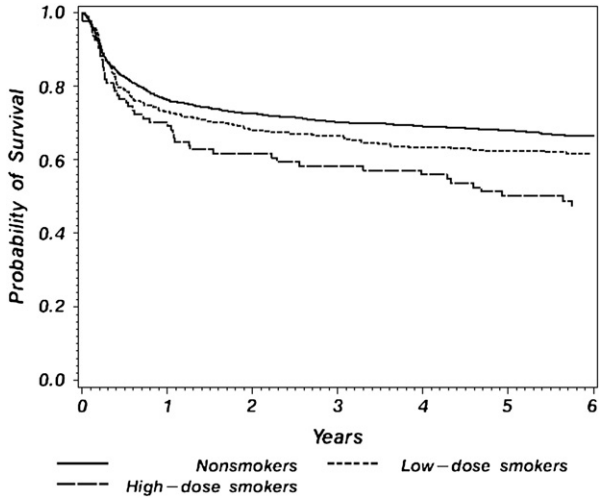

Figure 1. Probability of OS of patients ≥18 years receiving HLA-identical siblings allogeneic transplants for CML in first chronic phase, reported to the CIBMTR, 1990-2004.

DISCUSSION

Smoking has profound effects on health, causing higher rates of malignancy, cardiac, and pulmonary disease [12]. Nonetheless, a significant percentage of transplant candidates will be PCS and physicians take smoking history as part of the pretransplant evaluation. Some regard smokers as inferior transplant candidates, and in borderline cases it may be a factor in the decision to proceed to transplant.

The major findings of this study are that in sibling allograft recipients high-dose smoking (>10 pack years and >1 pack/day [20% of smokers]) was associated with clinically and statistically significantly reduced DFS and OS compared to NS. The absolute magnitude of the reduction in survival of 18% is important, and both transplanters and high-dose smoking patients should be aware of these data. This effect is mediated by a higher TRM (50% versus 28%), and although the RR of relapse was higher in smokers overall, it was not increased in the high-dose group. Analysis of univariate outcomes (Table 3) suggested an effect on IP ($P = .018$), but no effect on bronchopneumonia or bronchiolitis obliterans. The effects of smoking on TRM may not be just pulmonary, as smoking has the potential to affect the function of other vital organs. Despite these findings we are not advocating that transplanters should withhold this therapy from this patient subset nor should it affect a patient's health insurance status. Future research should focus on reducing the higher TRM in the high-dose smoking group. Reduced-intensity conditioning (RIC) is one possible way of achieving this. We did not see significant effects on TRM and survival in the lower dose smoking group; this is biologically plausible, but a prospective study would be of value in clarifying this finding. It is worth noting that there were no major differences in outcome in the recipients of unrelated donor transplants; it is possible that the higher TRM associated with unrelated transplantation masked a separate effect of smoking. Small numbers in the high-dose group reduced the chance of demonstrating significant differences.

Table 4. Multivariate Analysis Comparing Outcomes among Patients ≥18 Years Old Receiving Transplants for CML in First Chronic Phase, Reported to the CIBMTR, 1990-2004

Variables	N	Relative Risk (95% CI)	*P*-Value
HLA-identical sibling donor			
Relapse*			
Nonsmoker	1563	1.00	.008
Past/current smoker†			
Low dose	347	1.75 (1.23-2.49)	.002
High dose	88	1.02 (0.44-2.36)	.960
Treatment-related mortality‡			
Nonsmoker	1563	1.00	.008
Past/current smoker			
Low dose	347	0.95 (0.77-1.88)	.657
High dose	88	1.57 (1.14-2.14)	.005
Disease-free survival§			
Nonsmoker	1563	1.00	.012
Past/current smoker			
Low dose	347	1.14 (0.95-1.37)	.162
High dose	88	1.52 (1.14-2.04)	.005
Overall survival¶			
Nonsmoker	1563	1.00	.049
Past/current smoker			
Low dose	370	1.01 (0.84-1.22)	.910
High dose	94	1.44 (1.07-1.93)	.015
Unrelated donor transplants			
Relapse⊥			
Nonsmoker	514	1.00	
Past/current smoker	149	0.67 (0.28-1.56)	.351
Treatment-related mortality**			
Nonsmoker	514	1.00	
Past/current smoker	149	1.02 (0.79-1.33)	.861
Disease-free survival††			
Nonsmoker	514	1.00	
Past/current smoker	149	0.97 (0.76-1.25)	.834
Overall survival‡‡			
Nonsmoker	544	1.00	
Past/current smoker	161	0.96 (0.75-1.21)	.708

CI indicates confidence interval; CML, chronic myelogenous leukemia; GVHD, graft-versus-host disease; CIBMTR, Center for Internatioinal Blood and Marrow Transplant Research; WBC, white blood cells.

*Relapse model adjusted for recipient age, gender, region, spleen size at diagonosis, and GVHD prophylaxis.

†Low-dose smokers = smoking ≤10 pack-years or >10 pack-years with ≤ 1 pack/day; high-dose smokers = smoking >10 pack-years with >1 pack/day.

‡TRM model adjusted for recipient age, sex, region, karnofsky score, GVHD prophylaxis, WBC count, EBMT risk score, and graft sources. Stratified on conditioning regimen/dose group.

§DFS model adjusted for recipient age, sex, region, karnofsky score, GVHD prophylaxis, and time from diagnosis to transplant. Stratified on conditioning regimen/dose group.

¶Overall survival model adjusted for recipient age, sex, region, Karnofsky score, GVHD prophylaxis, EBMT risk score, and graft sources. Stratified on conditioning regimen/dose group.

⊥Relapse model adjusted for recipient age, sex, and region.

**TRM model adjusted for recipient age, sex, region, recipient CMV, GVHD prophylaxis, and EBMT risk score.

††DFS adjusted for recipient age, sex, region, recipient CMV, GVHD prophylaxis, and EBMT risk score.

‡‡Overall survival model adjusted for recipient age, sex, region, recipient CMV, year of transplant, GVHD prophylaxis, and EBMT risk score.

Table 5. Reported Causes of Death of Patients ≥18 Years Receiving HLA-Identical Sibling Donor Transplants for CML in First Chronic Phase, Reported to the CIBMTR, 1990-2004

		Smokers	
	Nonsmokers	Low Dose	High Dose
Causes	N (%)	N (%)	N (%)
GVHD	132 (24)	32 (23)	9 (18)
IPN	95 (18)	24 (17)	9 (18)
Infection	103 (19)	31 (22)	13 (25)
New malignancy	5 (1)	5 (4)	1 (2)
Organ failure	53 (10)	14 (10)	9 (18)
Other cause	80 (15)	20 (14)	8 (16)
Primary disease	73 (13)	15 (11)	2 (4)

GVHD indicates graft-versus-host disease; IPN, interstitial pneumonitis; CIBMTR, Center for International Blood and Marrow Transplant Research; CML, chronic myelogenous leukemia.

Smoking may also have had an effect on relapse; however, this was only seen in low-dose smokers (RR = 1.75) on multivariate analysis. The lack of an effect in high-dose smokers may result from the higher TRM in this group. The apparent effect in low-dose smokers was not because of RIC or via an effect on GVHD. Smoking may be immunomodulatory (inflammatory bowel disease is more common in smokers) [13]; donor T cells may be rendered less able to mediate a graft-versus-leukemia (GVL) effect. However, we do not have data about smoking posttransplant. A mouse model showed effects on dendritic cells and on T cell proliferation [14]. The smoking status of the donor might be of greater importance in this effect, and there is a high incidence of smoking in the siblings of smokers [15]. This could explain the fact that there was no increase in relapse in unrelated donor recipients who tend to be healthy and smoke less. However, the minority of smokers who continue to smoke posttransplant may affect the donor T cells on a continuing basis. In a study from Boston [16] the risk of relapse appeared to be higher in smokers and increased with each pack year of exposure. In that study, 14 of 17 patients who had relapse smoked ($P = .01$). The same group, however, found no effect of smoking on 1-year survival [17].

Table 6. Reported Causes of Death of Patients ≥ 18 Years Receiving Unrelated Donor Transplants for CML in First Chronic Phase, Reported to the CIBMTR, 1990-2004

		Smokers	
	Nonsmokers	Low Dose	High Dose
Causes	N (%)	N (%)	N (%)
GVHD	60 (21)	18 (24)	7 (33)
IPN	59 (20)	9 (12)	5 (24)
Infection	79 (27)	17 (23)	2 (10)
New malignancy	3 (1)	1 (1)	1 (5)
Organ failure	27 (9)	14 (19)	2 (10)
Other cause	43 (15)	8 (11)	3 (14)
Primary disease	20 (7)	8 (11)	1 (5)

GVHD indicates graft-versus-host disease; IPN, interstitial pneumonitis; CIBMTR, Center for International Blood and Marrow Transplant Research; CML, chronic myelogenous leukemia.

Additionally, there may be effects on pulmonary function, although reports vary. Twenty years ago the Seattle group [18] found that smoking was associated with a lower FEV_1/FVC at 1 year posttransplant ($P = .01$); the effect on pulmonary function tests (particularly gas transfer) at 1 year was confirmed by a French group [19]. Gas transfer was impaired at baseline and during the first year posttransplant in smokers, including in transplants with non-TBI conditioning [20]. Savani and colleagues [3] found that smoking increased TBI-related pulmonary mortality 5-fold, but that this effect could be reduced by giving a high CD34 dose. However, effects on pulmonary outcomes were not seen after all studies. Ho and colleagues [4] from Boston found no increase in severe pulmonary complications posttransplant.

This study has limitations that should influence data interpretation. First, the registry forms did not capture whether the smoking was current or past or if smoking was resumed after transplant. Second, we had limited "dose" data and could not calculate pack years accurately in many cases, which may explain the inconsistent dose-related findings. Third, the self-reported smoking history may be inaccurate and there may be some underreporting. Fourth, knowledge of the demographic factors that are associated with smoking [21] would have improved our ability to make conclusions. Finally, in retrospect, it might have been informative to examine outcomes in other transplant eligible diseases, as smoking may have more effect in patients who had substantial pretransplant chemotherapy. In many countries fewer patients with early phase CML proceed to transplant now; however, the EBMT risk score for CML has been validated for other diseases, and it seems likely that the effect seen in CML patients would also be seen in patients with other hematologic malignancies. Patients with diseases such as acute leukemia are exposed to recurrent episodes of neutropenia, which has the potential to augment some of the organ-related effects of smoking including pulmonary infection.

Further examination of this issue would require a prospective study; this would have several advantages. There would be more accurate correlation of past and current exposure of patients and their donors with outcome, and this could be associated with regular pulmonary function tests. There would also be the opportunity to collect patient-reported outcomes and determine if there are effects on rehospitalization, chest infections, and reemployment. Furthermore, prospective demographic data could be collected, allowing the study to separate the effects of smoking from effects that the different demographic characteristics

that smokers may have. Nonetheless, this study presents clinically important findings. It is the largest study ever that examines the impact of smoking on transplant outcome, and contains data that patients and transplanters will be able to use in making clinical decisions.

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